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SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402-0938

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/636,053	KUCHARCZYK, KRZYSZTOF	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed August 7, 2003. Currently, claims 1-13 are pending.

Priority

2. This application claims priority to PCT/PL01/000012, filed February 7, 2001.

Drawings

3. The drawings are acceptable.

Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

For example, on page 37, 39, the specification contains sequences which are not identified by SEQ ID NO:. Appropriate correction is required.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-13 are indefinite since Claim 1 does not appear to be a complete claim. Claim 1 does not end in a period and appears to be missing a clause following "and." Therefore, it is unclear what additional steps and limitations are required for the instant claims.

B) Claims 1-13 are indefinite over the recitation "the single strand special conformers" in step b and "the native separation" in step c because each of these recitations lack proper antecedent basis. The claims do not set forths a single strand spatial conformer. Further, the claims do not provide an active separation step. Thus, each of these recitations lack proper antecedent basis.

C) Claim 3 is directed to "wherein said changed the physical parameter..." This recitation does not make grammatical sense.

D) Claims 3-5 are directed to "said changed physical parameter" however the claims do not refer to any "physical parameter." The claims are directed to changing the physical conditions during the native separation. It is unclear whether the physical condition is what is being referred to as "said changed physical parameter."

E) Claim 5 is directed to any combination of parameters like: temperature, pH, ionic strength and the like. It is unclear whether the list is limited to these particular parameters and also what "the like" encompasses. The metes and bounds of the claimed invention are unclear. Regarding claim 5, the phrase "or the like" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "or the like"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

F) Claim 6 is indefinite because it is unclear if a single stranded nucleic acid is started with how you would transform the nucleic acid into single stranded nucleic acid spatial conformers. Thus, the metes and bounds are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-5, 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (Nucleic acids Research, Vol. 23, No. 21, pages 4524-4525, 1995).

It is noted that Claim 1 is not a complete claim. The claim ends with "and" which is not a complete sentence and does not end in a period.

Chen et al. (herein referred to as Chen) teaches a method for detecting a variation in a nucleic acid molecule by providing a nucleic acid, transforming or denaturing the nucleic acid into a single stranded conformers (strands), separating the single stranded nucleic acids under native conditions, and changing one or more conditions. Chen specifically teaches that in non-denaturing conditions, ssDNA has a folded structure that is determined by its nucleotide sequence. The sequence changes as small as single nucleotide substitutions may alter the structure and thereby the gel electrophoretic mobility such that they can be identified as a band shift in gel electrophoresis. Chen uses an example of the potato spindle tuber viroid which is the

smallest plant pathogen and consists of a single-stranded, circular and autonomously replicating RNA molecule (limitations of Claim 8). Chen teaches amplifying a nucleic acid with PCR, denaturing the products prior to loading the nucleic acids, electrophoresing the DNA at 300 V for 10 minutes at temperature of 15C and for 2.5 h in presence of the gradient from 20-55 (limitations of Claim 4-5). The gel was analyzed for detection patterns (see Figure 1). Chen also teaches that analysis of wild-type and variants was performed (Figure 2). A two-temperature SSCP gel electrophoresis demonstrates that wild type and mutant nucleic acids are separated by electrophoresis on a gel. The electrophoresis was carried out for 4 hours at 23C and for 1 hour at 43C (limitations of Claim 4-5). The 23C separated M1, M2 and M6 then the 43C was used to separate M3, M4, M5 and M7. All 8 variants (see Figure 2A) which included SNPs which are mutations could be clearly separated (page 4525, col. 2) (limitations of Claim 2-3). Chen teaches that temperature, ionic strength, denaturant, and buffer concentration have all been shown to alter ssDNA mobility (page 4524, col. 1). Therefore, Chen teaches every limitation of the instant claims and anticipates the claimed invention.

7. Claims 1-7, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Sugano et al. (Electrophoresis, Vol. 16, pages 8-10, 1995).

Sugano et al. (herein referred to as Sugano) teaches a method for detecting a variation in a nucleic acid molecule by providing a nucleic acid, transforming or denaturing the nucleic acid into a single stranded conformers (strands), separating the

single stranded nucleic acids under native conditions, changing one or more conditions of the separation and detecting the mobility pattern. Specifically, Sugano teaches a method of temperature-gradient gel electrophoresis for analyzing K-ras and p53. Sugano teaches TG-SSCP establishes a temperature gradient ranging from 5C- 45C during electrophoresis. Sugano teaches that amplified DNA fragments of c-Kiras2 gene were electrophoresed. PCR used genomic DNA, denatured with 90% formamide and heated to 80C and run on the polyacrylamide gel. Sugano teaches dissociating the PCR product into two ssDNA bands (limitations of Claim 6-7). The temperature gradient over the gel changes the conditions of the separation. As seen in Figure 2a, b, c, the gels illustrate temperatures in which variations may be detected (page 9). The gels were subjected to silver staining (page 9, Figure 2 legend)(limitations of Claim 13). The mutation analyzed in Figure 2 is a GGT to a GTT (a single nucleotide polymorphism). Sugano teaches that the temperature of the gel during electrophoresis is an important parameter in optimization since conformation of ssDNA fragments strongly depends on gel temperature. Sugano teaches every limitation of the instant claims therefore, Sugano anticipates the claimed invention.

8. Claims 1-7, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Rubben et al. (Eur. J. of Epidemiology, Vol. 11, pages 501-506 1995).

Rubben et al. (herein referred to as Rubben) teaches a method of non-radioactive temperature gradient SSCP analysis for the detection of HPV variants. Rubben teaches that in SSCP, single stranded nucleic acids are separated in a

nondenaturing polyacrylamide gel so sequence mutation can be detected. Rubben teaches that electrophoresis applying a temperature gradient should enhance the possibility that one DNA fragment adopts a conformation which differs from the homologue DNA resulting in a different migration pattern (page 502, col. 1). Rubben teaches that tissue specimens were obtained from patients (page 502, col. 1). For TG-SSCP, DNA templates were generated by PCR using primers. The product was mixed with formamide and denatured at 100C. Electrophoresis was performed in a gel matrix with a temperature gradient. The nucleic acids were stained with silver (page 502, col. 2)(limitations of Claim 13). Rubben teaches sequencing the most frequent variants by dideoxy sequencing (page 502, col. 2). As seen in Figure 1, TG-SSCP was performed at different temperatures for HPV 6b (a control) and two patients. The major variants detection are illustrated in Table 2 (page 504). Rubben teaches every limitation of the instant claims, therefore, Rubben anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Sugano et al. (Electrophoresis, Vol. 16, pages 8-10, 1995) or Rubben et al. (Eur.

J. of Epidemiology, Vol. 11, pages 501-506 1995) in view of Wallace (Laboratory methods for the detection of mutations and polymorphisms in DNA, 2000, pages 79-94).

Sugano et al. (herein referred to as Sugano) teaches a method for detecting a variation in a nucleic acid molecule by providing a nucleic acid, transforming or denaturing the nucleic acid into a single stranded conformers (strands), separating the single stranded nucleic acids under native conditions, changing one or more conditions of the separation and detecting the mobility pattern. Specifically, Sugano teaches a method of temperature-gradient gel electrophoresis for analyzing K-ras and p53. Sugano teaches TG-SSCP establishes a temperature gradient ranging from 5C- 45C during electrophoresis. Sugano teaches that amplified DNA fragments of c-Kiras2 gene were electrophoresed. PCR used genomic DNA, denatured with 90% formamide and heated to 80C and run on the polyacrylamide gel. Sugano teaches dissociating the PCR product into two ssDNA bands (limitations of Claim 6-7). The temperature gradient over the gel changes the conditions of the separation. As seen in Figure 2a, b, c, the gels illustrate temperatures in which variations may be detected (page 9). The gels were subjected to silver staining (page 9, Figure 2 legend)(limitations of Claim 13). The mutation analyzed in Figure 2 is a GGT to a GTT (a single nucleotide polymorphism). Sugano teaches that the temperature of the gel during electrophoresis is an important parameter in optimization since conformation of ssDNA fragments strongly depends on gel temperature.

Rubben et al. (herein referred to as Rubben) teaches a method of non-radioactive temperature gradient SSCP analysis for the detection of HPV variants.

Rubben teaches that in SSCP, single stranded nucleic acids are separated in a nondenaturing polyacrylamide gel so sequence mutation can be detected. Rubben teaches that electrophoresis applying a temperature gradient should enhance the possibility that one DNA fragment adopts a conformation which differs from the homologue DNA resulting in a different migration pattern (page 502, col. 1). Rubben teaches that tissue specimens were obtained from patients (page 502, col. 1). For TG-SSCP, DNA templates were generated by PCR using primers. The product was mixed with formamide and denatured at 100C. Electrophoresis was performed in a gel matrix with a temperature gradient. The nucleic acids were stained with silver (page 502, col. 2)(limitations of Claim 13). Rubben teaches sequencing the most frequent variants by dideoxy sequencing (page 502, col. 2). As seen in Figure 1, TG-SSCP was performed at different temperatures for HPV 6b (a control) and two patients. The major variants detection are illustrated in Table 2 (page 504). Neither Sugano nor Rubben specifically teach detecting the nucleic acid using a fluorescent label, or an electromagnetic label.

However Wallace teaches general methods for SSCP mutation detection. Wallace teaches fragment labeling and visualization was originally via radioisotope labeling and autoradiography. These methods were substituted with nonisotopic methods including ethidium bromide staining, silver staining and florescence labeling (page 79-80). Wallace teaches that is it possible to pool two or more samples and amplify them simultaneously (page 83)(limitations of Claim 40).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the silver staining detection method of

Sugano or Rubben with any of the alternative methods of detecting and visualizing the nucleic acid upon the gel. The ordinary artisan would have recognized that any method which allowed for visualization could be used in the method of detecting migration of nucleic acids within a gel.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 3-5, 7-41, 57-79 of U.S. Application No. 10/212,486.

An provisional obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046,

29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentable distinct from each other because Claims 1-13 of the instant application is generic to all that is recited in Claims 1, 3-5, 7-41, 57-79 of U.S. Application No. 10/212,486. The instant claims are drawn to a method for detecting a variation in a nucleic acid by providing a nucleic acid, transforming the nucleic acid, separating the nucleic acid, changing a condition of the separation during the separation and detecting the mobility pattern. Claim 1 of application the instant application is directed to detecting a difference at a target nucleic acid by providing a nucleic acid, transforming the nucleic acid, changing the physical conditions during the separation of the single stranded conforms at least one time. The claims require nearly identical steps. The claims of the '486 application are directed to detecting a variation in a nucleic acid molecules by providing nucleic acid, transforming the nucleic acid into one or more single stranded nucleic acid, separating under native conditions, changing one or more conditions of the separation at least twice during the separation and detecting mobility patterns where the condition is temperature and the temperature is lowered during the separation. Therefore, since each of the instant claims would be anticipated by Claims 1, 3-5, 7-41, 57-79 of U.S. Application No. 10/212,486, a double patenting rejection is appropriate.

Conclusion

11. No claims allowable over the art.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Liu et al. (US Pat. 6,287,411, September 11, 2001) teaches multi conditional SSCP for mutation scanning at virtually 100% sensitivity. Liu tests various parameters such as temperature, ph and gel matrix.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
July 11, 2005